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HORMONAL CONTROL OF
NEOPLASTIC GROWTH*

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WHEN the Fortnight Committee invited me to discuss for you the topic of "Hormonal Control of Neoplastic Growth," I recognized the vastness of the topic, but welcomed the opportunity to discuss this subject because of the newer concepts concerning cancer, which are arising from these studies. As a medical student, I was taught that cancer is an autonomous parasitic growth, which is completely beyond any physiologic controls. As a result of the many studies which are reported in the literature and which are now in progress in many laboratories, I believe that we can now challenge that old concept. Indeed I believe that studies on the relationship of hormones to the development of tumors or to the inhibition of certain metastatic neoplasms make it possible now for us to foster a real hope for eventual control of these diseases by physiologic means.

The medical and biological literature of the last decade and a half is replete with experimental and clinical studies on the relationship of hormones to neoplasms. Such intense activity in this field during the past

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fifteen years can be attributed to the availability of potent synthetic and natural hormones and experimental tools and techniques not previously available. To review by brief reference to this vast literature would require much more time than that allotted me. There are, however, excellent reviews on this subject by Loeb,¹ Gardner,² Shimkin³ and Nathanson⁴ which I can recommend to you.

Before discussing some of the modern studies, it should be pointed out that in 1889 Schinzinger,⁵ a German surgeon, advocated oophorectomy in premenopausal women with cancer of the breast because of the atrophy of the breast which follows loss of ovarian function. Several years later in 1896 Beatson,⁶ a surgeon from Glasgow, reported striking beneficial changes in two premenopausal women with extensive and metastatic cancer of the breast whom he had oophorectomized and treated with thyroid.

HORMONAL FACTORS IN THE PRODUCTION OF TUMORS IN EXPERIMENTAL ANIMALS

The first carefully planned and executed study of the glands of internal secretion and their relationship to cancer was that reported in 1919 by Dr. Leo Loeb.⁷ He demonstrated in mice having a high incidence of breast cancer that ovariectomy of the young prevented the development of mammary cancer. Castration after the age of six months had practically no effect on the development of these tumors.

In 1932, Lacassagne⁸ first succeeded in producing carcinoma of the mammary gland in male mice belonging to high tumor strains by injecting large amounts of estrogenic hormones over long periods of time. Negative results were obtained when estrogens were administered to male mice belonging to strains in which spontaneous mammary tumors in the females are uncommon. These experiments were confirmed very promptly by Burrows,⁹ and Gardner, Smith, Allen and Strong.¹⁰

Since that time there have been many reports of tumors produced in animals after prolonged treatment with various estrogenic compounds both steroidal and non-steroidal.

Lacassagne¹¹ has demonstrated that the influence of various estrogens on the formation of breast tumors in mice appears to be proportional to their estrogenic activity. Gardner¹² has reported that the administration of estrogens to hybrid mice from matings of high tumor strains and low tumor strains resulted in a high incidence of tumors in mice

whose mothers were of the high tumor strain but not in those whose mothers were of a low tumor strain.

Gardner, Allen, Smith and Strong¹³ reported in 1938 the appearance of a metastasizing transplantable cancer of the cervix in a mouse of a high tumor strain following the injection of estrogens for ten months. Subsequently, Allen and Gardner¹⁴ have produced several cancers of the cervix in two groups of hybrid mice.

Lipschütz, Rodriguez and Vargas¹⁵ have reported that the administration of estradiol monobenzoate to guinea pigs resulted in the development of uterine and extrauterine fibroids and endometrial polyps which extended into the vagina. They¹⁶ have reported subsequently that the simultaneous administration of testosterone or progesterone with the estrogen prevented the development of such uterine fibroids.

Gardner, Dougherty and Williams¹⁷ studied the lymphoid tissues of seven strains of mice receiving estrogens over a long period of time. In three strains (C₃H, CBA, P.M.) they observed 15 per cent incidence of lymphosarcomas, in the other strains (C₁₂1, JK, A and C₅₇) they observed an incidence of 2 to 5 per cent. It is of interest that the simultaneous administration of testosterone with estrogens in one of the more susceptible strains resulted in an apparent inhibition to the development of such lymphoid tumors.

Hooker and Pfeiffer¹⁸ have reported that the administration of estradiol benzoate or of stilbestrol to male mice of the A strain resulted in the development of interstitial cell tumors of the testes which apparently were capable of producing androgens. They postulated that the mechanism of this tumor's genesis was through a stimulatory effect on the pituitary's production of luteinizing hormone, which in turn acted to stimulate growth of the Leydig cells.

Woolley and his associates^{19,21} have followed male and female mice of several strains, which were castrated between one and six months of age. In these animals they have observed hyperplasia and neoplastic changes in the adrenal cortices. Some of these tumors were observed to exert androgenic effects on the hosts and others exerted estrogenic effects. In several of their mice tumors of the mammary glands and of the pituitaries were observed after the development of the adrenal tumors. At present, we have a patient on the research ward of the James Ewing Hospital, who presents a similar situation. This female patient has had both breasts removed for malignant tumors. She now

has the picture of a functioning tumor of the adrenal cortex. We might speculate as to the possibility of the adrenal tumor having hormonal effects on the breasts which resulted in tumors.

Leo Loeb was the first investigator who explored the role of the pituitary in the development of mouse tumors. In 1939, Loeb and Kirtz²² reported that they had successfully transplanted pituitaries of inbred mice to their siblings. Such transplants caused marked development and secretory activity in the mammary glands. They caused a marked increase in the incidence of mammary cancer in females of the A strain over that observed in virgin mice without transplants. In a small number of mice with transplants of the anterior pituitary, precancerous changes were observed in the vaginal cervical tract.

In 1941 Evans and his associates²³ reported that the administration of pituitary extracts rich in gonadotropic hormones caused placentomas in normal but not in hypophysectomized rats. A pituitary preparation rich in lactogenic hormone favored the production of such tumors in normal, adrenalectomized or hypophysectomized rats, but not in ovariectomized animals.

More recently, in a series of important studies, Moon and associates²⁴⁻²⁶ have reported that the prolonged administration of growth hormone to intact rats of the Long Evans strain resulted in the development of lymphosarcomas of the lung and of the peribronchial lymph nodes, in solid tumors of the ovaries and in atypical hyperplasia of the ovarian follicles which resembled granulosa or interstitial cell tumors of the ovary. Fibroadenomata of the breast occurred more often and were larger than in the untreated controls. In the adrenals of these animals the adrenal cortices showed nodular changes and the medullae were hypertrophic and proliferative with areas of neoplastic cells invading and displacing the adrenal cortices. In three rats the neoplastic medullary tissue grew through the cortex and was macroscopically visible on the surface of the adrenal gland.

The pituitaries of these animals were found to contain smaller, less granular and fewer acidophils than those of the controls, while the basophils were increased in number and resembled those observed in castrate rats. In one rat, the pituitary contained numerous small basophilic adenomata.²⁷

It is of interest that the administration of growth hormone to hypophysectomized rats of the same strain resulted in a normal growth

response but failed to produce any neoplastic changes.²⁸ This obviously suggests that some other pituitary hormone or a hormone of the target gland of some other pituitary hormone is necessary to the development of such tumors. More recently these same investigators²⁹ have reported that the development of cancers in response to treatment with methylcholanthrene is markedly diminished in hypophysectomized rats.

During the past decade, we have had a variety of goitrogenic agents made available. These agents are goitrogenic by virtue of two actions, i.e., secondary to a hypothyroidism, which they produce, they cause an increased secretion of TSH by the pituitary, and they enhance the action of TSH. With these agents at hand, several investigators have administered them to rats or mice over long periods of time. In 1944, Bielschowsky^{30,31} reported that the administration of 2-acetyl-amino-fluorine and allyl thiourea to rats resulted in the production of thyroid tumors, both benign and malignant. Shortly afterwards, Griesbach, Kennedy and Purves³² reported that the administration of a rape seed diet resulted in the development of hyperplastic goiters which later manifest tumors of the thyroid. More recently, these same investigators³³ have produced a highly malignant cancer of the thyroid by administering methyl thiouracil to their rats.

Dalton, Morris and Dubnik^{34,35} have reported that the administration of thiouracil to mice of a high tumor strain resulted in the development of metastasizing and transplantable cancers of the thyroid, whereas the same agent when administered to mice of a low tumor strain, produced hyperplasia and benign tumors of the thyroid. Money and Rawson³⁶⁻³⁸ have observed that the administration of thiouracil to rats of the Sprague-Dawley strain resulted in a variety of benign adenomas. When they combined thiouracil with subcutaneous injections of dibenzanthracene, they were able to produce a transplantable cancer of the thyroid. It is concluded that such cancers are dependent on the growth stimulus of the pituitary thyroid stimulating hormone and upon an inherited cancer susceptibility or the action of a carcinogen.

OBSERVATIONS SUGGESTING POSSIBLE HORMONAL FACTORS IN GENESIS OF HUMAN CANCER

It would be premature to conclude from the above experimental observations that these various hormones are a cause of cancer as seen in man. However, it would be quite unsound to discard them as of no

consequence in human studies. Indeed there are several clinicopathologic states, recently described by thoughtful and observing students which give credence to the theory that similar situations might apply in man.

In 1922, Schröder of Rostock³⁹ reported a forty-five year old patient in whom he had found a large granulosa cell tumor of the ovary, which was associated with endometrial hyperplasia and an early carcinoma of the endometrium. Dockerty⁴⁰ and Hodgson, Dockerty and Mussey⁴¹ have reported a variety of pathologic lesions which co-existed with granulosa cell tumors in sixty-two patients seen at the Mayo Clinic. Thirty-two (51.6 per cent) of these feminizing tumors were associated with uterine fibromyomata, eight (or 12.9 per cent) with carcinoma of the uterine fundus and three (or 4.8 per cent) with carcinoma of the breast. Banner and Dockerty⁴² have reported that in twenty-three patients with theca cell tumors myohypertrophy and/or fibromyomas were found in thirteen, endometrial adenocarcinoma in three, adenocathanthoma of the cervix with metastases in one and epidermoid carcinoma of the cervix in one. More recently Dockerty and Mussey⁴³ have reported that the incidence of endometrial cancer in a series of eighty-seven patients with granulosa cell or theca cell tumors was more than 15 per cent. In three of their patients endometrial and breast carcinomas were found to exist or to occur shortly after the ovarian tumors had been removed. Smith⁴⁴ has stated that 1/5 of his patients with granulosa cell tumors also had endometrial cancers. Smith⁴⁵ has also noted a cortical stromal hyperplasia in the ovaries of 80 per cent of his postmenopausal patients with endometrial cancer. This cortical stromal hyperplasia has been described as an increased thickness and cellular density in the cortical stroma with numerous whorls and interlacing fascicles weaving about variable numbers of capillaries and dipping irregularly into the relatively cellular eosinophilic medullary stroma. Enlarged nuclei with abundant coarse granular chromatin have been described in these cortical stromal cells. Because these structures take fat stains it has been suggested that they represent estrogen secreting tissue. In subsequent studies by Woll, Hertig, Smith and Johnson⁴⁶ the incidence of cortical stromal hyperplasia in patients with endometrial cancer was found to vary in various decades between 56 and 92 per cent whereas for a control age group it was found to vary between 36 and 43 per cent. These investigators also reported that thecomas in patients with endometrial cancer are 9 times

as common as in a control group.

Sommers and Teloh⁴⁷ have reported that cortical stromal hyperplasia was observed in 83 per cent of 100 autopsied patients with cancer of the breast as opposed to an incidence of 37.5 per cent in a control group. In a subsequent report McManus and Sommers⁴⁸ suggested that the therapeutic effects of castration for metastatic cancer of the breast in patients shown to have cortical stromal hyperplasia are better than they are in patients whose ovaries do not show cortical stromal hyperplasia.

Data from the Canton of Zurich, Switzerland,⁴⁹ where the death rate from thyroid cancer has decreased subsequent to the use of iodized salt, would suggest a similar relationship between thyroid neoplasia and goitrogenesis, presumably mediated via the pituitary in the human, as has been demonstrated in rats. In this canton, iodized salt was first introduced in 1923. Its use had gradually increased to 90 per cent by 1950. The incidence data for deaths from cancer of the thyroid per 100,000 for males and females were as follows: 1906-1915, 2.04 and 1.43; 1916-1925, 2.12 and 1.59; 1926-1935, 1.40 and 1.74; 1936-1945, 0.65 and 0.94. This marked decrease in cancer of the thyroid strongly suggests that prophylaxis of goiter is a prophylaxis against cancer of the thyroid. Presuming that goitrogenesis in humans is mediated as in rats by the patient's increased production of TSH, we might suggest that TSH contributes to the genesis and growth of thyroid cancer.

Unfortunately, our techniques for demonstrating gonadal or pituitary hormones in blood or urine are still quite inadequate and we are unable to report on the metabolism of ovarian or pituitary hormones. However, the late Dr. Konrad Dobriner of the Sloan-Kettering Institute and Dr. Seymour Lieberman now of the College of Physicians and Surgeons have reported^{50, 51} extensive studies on the urines of normal humans and patients with various neoplastic diseases. In these studies, they have concentrated on a separation of the various steroids in the urine. The major steroids isolated by them from the urines of normal men and women were androsterone, etiocholanolone, 11-hydroxy-androsterone and 11-keto-etiocholanolone. In the urine of patients having a variety of cancers, they demonstrated another steroid which they very seldom found in normal humans, 11-hydroxy-etiocholanolone. This steroid, because of its structure, is thought to be a metabolite of one of the adrenal steroids, normal or abnormal.

EXPERIMENTALLY INDUCED HORMONAL CONTROL OF HUMAN CANCER

A third approach to this problem is found in the clinical experiments in which attempts have been made to affect the course of certain human cancers by altering the hormonal environment.

The sequence of events, which led to the endocrinologic studies in patients with metastatic carcinomas of the prostate is one of the most fascinating accounts in experimental medicine. In 1936, the Gutmans of the College of Physicians and Surgeons⁵² reported that they had found a high titer of phosphatase in the metastases of a patient who had carcinoma of the prostate, which reacted only at an acid pH level. Subsequent studies by the Gutmans⁵³ and by Woodard⁵⁴ demonstrated an elevated acid phosphatase level in the blood of patients with metastatic cancer of the prostate. The Gutmans⁵⁵ then demonstrated that this enzyme is present in normal prostates, and that it could be increased in the prostates of monkeys by administering testosterone.⁵⁶

Studies done by Huggins and associates^{57, 58} at about the same time, demonstrated that prostatic secretion in dogs was decreased by castration. They also demonstrated that the administration of testosterone caused a regeneration of the prostate and that this could be inhibited by the administration of estrogens.

Huggins, Hodges and Stevens^{59, 60} then applied these physiologic considerations in the treatment of patients with metastatic cancer of the prostate. They castrated twenty such patients and observed an appreciable clinical improvement in fifteen patients. There was a fall in the serum acid phosphatase in all but two cases. There was an increase in body weight and an increase in the hemoglobin levels. Shrinkage of the primary lesions was also observed. They also reported that the administration of testosterone to such patients resulted in an increase in the serum acid phosphatase whereas the administration of estrogenic hormones caused a fall in the blood levels of this enzyme.

These observations by Huggins have been widely confirmed during the past decade. An analysis of pooled cases, from fourteen clinics, which had received endocrine treatment, has recently been published by Nesbit and Baum.⁶¹ Of 115 patients with and without metastases on admission treated with diethylstilbestrol only 18.3 per cent survived five years. Twenty-six per cent of 359 cases treated by castration, and 36.3 per cent of 113 patients treated by castration and with diethylstil-

bestrol survived five years. Only 9 per cent of 504 untreated cases followed between 1925 and 1940 survived for five years.

In 1945 Huggins and Scott,⁶² who reasoned that relapses in patients who had made favorable responses following castration were due to androgens being elaborated by the adrenal, did bilateral adrenalectomies in four previously castrated patients who had later relapsed. Three of these patients died of adrenal insufficiency in the postoperative period. In one patient who survived for more than three months they reported that there was relief of pain and even shrinkage of the primary tumor. The fact that cortisone has recently been available in fairly adequate amounts has made it possible to expand studies on the effect of adrenalectomy in cancer of the prostate and other diseases. In 1952 Huggins and Bergenstal⁶³ reported their observations on seven patients with metastatic cancer of the prostate whose disease had relapsed following previous responses to anti-androgenic therapy. One patient died post-operatively. In four patients some of the following effects were observed: relief of intractable bone pain, gain in body weight, and a reduction in acid phosphatase. In two patients there was a significant shrinkage of large nodular prostates. In two patients no improvement whatsoever was observed.

West, Hollander, Whitmore, Randall, and Pearson⁶⁴ have studied the effect of adrenalectomy in eleven patients with advanced carcinoma of the prostate who had relapsed after previous response to castration and estrogen therapy. Transient relief of pain was observed in ten of their patients. Shrinkage of tumor tissue was observed in two of their patients. Unfortunately, objective improvement was not observed in any more of their cases.

Notwithstanding the theory originally advanced by Huggins that the benefit of castration and now of adrenalectomy in these patients is due to removal of the body's two major sources of testosterone and other androgens, it has been demonstrated by Brendler, Chase and Scott⁶⁵ and by Hollander and Whitmore⁶⁶ that the administration of testosterone is followed by exacerbation of the disease in only a fraction of the cases. Hollander and Whitmore⁶⁶ have observed in twenty-two patients with metastatic prostatic cancer that testosterone caused a rise in acid phosphatase in only nine cases and an increase in symptoms in only five cases. It would appear then that we may have to look for some other mechanism with which to explain these well-eslab-

lished therapeutic effects of castration in prostatic cancer.

It was stated earlier that Schinzinger,⁵ a German surgeon was the first to suggest castration for cancer of the breast. Beatson⁶ a surgeon from Glasgow, reported in 1896 having castrated two young women with advanced metastatic cancer of the breast. He reported relief of pain and regression of the cancerous growths in these patients. Following Beatson's report, there were numerous reports of this type of treatment for mammary cancer. Then for nearly twenty-five years, there was no activity in this field. Between 1921 and 1930 several writers recommended roentgen castration of premenopausal women with cancer of the breast. In 1938, Dresser⁶⁷ reported on a series of fifty-seven patients, whose ovaries he had attempted to destroy with x-ray. He reported beneficial effects in thirty per cent of his cases. In 1945, Adair, Treves, Farrow and Scharnagel⁶⁸ reported observations on 335 women with advanced carcinoma of the breast, whom they had castrated, 304 by x-ray and thirty-one surgically. In this group they observed objective benefit in only 15 per cent. They concluded that castration in general exerts only a temporary beneficial effect. In cases which are improved, the growth process appears to be retarded for about two years. They also reported that castration in eight males with advanced carcinoma of the breast resulted in spectacular regressions of the disease. In 1948, Treves⁶⁹ reported the results of castration in thirteen male patients with advanced carcinoma of the breast. The results in this group were just as spectacular as in the previous series with regression of local lesions and healing of skeletal metastases.

In 1939, Nathanson⁷⁰ reported that prolonged administration of testosterone to female mice of a high mammary cancer strain resulted in a significant decrease in the number of mammary tumors which ultimately developed. Following this report, there appeared reports by Farrow and Woodard⁷¹ and by Fels⁷² on the treatment of metastatic cancer of the breast with testosterone. The former workers reported symptomatic improvement without objective evidence of benefit. The latter investigator reported improvement in one patient with regression in soft tissue and bony metastases. Notwithstanding the unspectacular results in some of the earlier reports, continued studies have resulted in greater understanding and significant therapeutic results in patients with metastatic cancer of the breast treated with testosterone.

In 1944, Haddow and associates⁷³ first described the use of synthetic

estrogens in the treatment of carcinoma of the breast and of other sites. In this country, Nathanson⁷⁴ was the first to demonstrate a therapeutic effect of estrogens in postmenopausal women with advanced mammary carcinoma. During the past eight years, several clinics have been actually studying the therapeutic effects of androgenic and estrogenic hormones on human mammary cancer.

The policy has been to administer testosterone propionate intramuscularly in doses of 50 to 100 mg. three times a week to menstruating or early postmenopausal patients. Estrogens are administered orally as ethinyl estradiol 1 mg. three times daily, or diethylstilbestrol 5 mg. three times daily to women who are ten or more years postmenopausal.

The results of such therapeutic programs in the breast clinic of Memorial Center⁷⁵ are as follows: In the testosterone treated patients: recalcification of osteolytic lesions has been observed in 19 per cent of 133 patients having osseous metastases. In 174 patients, with soft tissue disease, improvement, i.e., significant and measurable decrease in the size of palpable lesions and healing of ulcers has been observed in 22 per cent. A decrease in the size of pulmonary nodules has been observed in only two of forty-eight cases. In the estrogen series, twenty-eight per cent of thirty-six patients with osseous disease have shown recalcification of one or more lesions, 41 per cent of 111 patients had significant improvement in the soft tissue sites of disease, and 33 per cent of thirty-nine patients with pulmonary disease have shown shrinkage of the pulmonary metastatic nodules. Although there is considerable variability in the rate of response, most successfully treated cases demonstrate improvement within three months.

A study now in progress by members of the Breast Clinic and the Radiotherapy Service at Memorial Center suggests that the combination of x-ray therapy with hormonal treatment is more effective in promoting healing of osseous and soft tissue lesions than is either x-ray or hormonal treatment alone.

Therapy with testosterone often leads to troublesome virilization, hirsutism, deepening of the voice, acne, increased libido and clitoral hypertrophy. It may also be complicated by sodium and water retention necessitating diuretic measures.

Recently Huggins and Yuan Dao⁷⁶ have reported their observations in eight patients who had been adrenalectomized for advanced mammary cancer. There was one postoperative death. One male patient with

metastatic carcinoma of the breast who had failed to respond to castration done six months prior to the adrenalectomy showed a satisfactory regression of disease. There was no amelioration of the breast disease in three women with the disease. In three women with metastatic cancer of the breast there was significant shrinkage of the tumors following adrenalectomy. Unfortunately two premenopausal patients who showed favorable responses following adrenalectomy were oophorectomized at the time of adrenalectomy and thus cannot honestly be included in any evaluation of adrenalectomy as a therapeutic measure for this disease.

West et al.⁶⁴ have studied the effect of adrenalectomy in nine patients with advanced carcinoma of the breast, who had previously been treated by castration and steroids but had either failed to respond to such treatment or had relapsed following initial responses. Objective evidence of improvement was observed in three cases. There was shrinkage of soft tissue disease and evidence of improvement in skeletal lesions. The improvement, though striking, was only transient. However, it has been great enough to warrant further investigation for at least a better understanding of the mechanism involved in those patients who do respond to this procedure.

It might seem to be paradoxical, but beneficial effects have also been obtained from the administration of cortisone or of ACTH in patients with certain types of tumors. It was first demonstrated by Murphy and Sturm⁷⁷ and then by Heilman and Kendall⁷⁸ that the administration of Kendall's Compound E (now known as cortisone) to mice bearing lymphosarcomas resulted in a shrinkage of the tumors. Pearson and associates⁷⁹ reported in 1949 that the administration of cortisone or of ACTH to patients with certain lymphomatous diseases resulted in a spectacular shrinkage of the tumor masses with metabolic changes which reflected the rate and amount of tumor destruction. Cessation of hormonal administration is followed by prompt recurrence of the tumors. Subsequent studies have revealed that some patients with lymphosarcoma, chronic lymphatic leukemia, or multiple myeloma can be successfully treated repeatedly with either of these hormones or with 11-hydroxy-cortisone (Compound F). It has also been demonstrated that patients with these diseases can be carried on cortisone for prolonged periods of time and that the disease is held under control by such treatment if dosage of the hormone is adequate.⁸⁰

The same investigative group has also explored the therapeutic

effects of these hormones in acute leukemia and other neoplasms.^{79, 81} They observed that acute leukemia responds once or twice to such an altered hormonal environment. Other tumors have not been favorably affected by this form of treatment.

Recent studies have also demonstrated that many cancers of the thyroid can very effectively be brought under the control of certain physiologic mechanisms. Indeed a large percentage of metastatic tumors of the thyroid has been forced to function much as normal thyroid tissue does. Although it has been demonstrated⁸² that in 100 cancers of the thyroid forty-six possessed the capacity to concentrate radioactive iodine, none of these tumors was capable of concentrating any more than a fraction of the iodine trapped by normal thyroid tissue. However, in one half of a group of forty-five patients with metastatic cancer of the thyroid, it has been demonstrated⁸³ that ablation of the normal thyroid results in previously non-functioning metastatic lesions assuming the function of normal thyroid tissue, i.e., concentrating radioactive iodine, and even maintaining the patient in a euthyroid state. It has also been demonstrated that the administration of thyrotropic hormone will induce function in the tumors of about one-third of the cases studied. Finally, it has been demonstrated in 70 per cent of a series of thirty-six previously totally thyroidectomized patients having skeletal or pulmonary metastases that the prolonged administration of thiouracil or of tapazol, agents which augment the action of thyrotropic hormone, results in the metastatic lesions acquiring maximum capacity to concentrate radioactive iodine. From the practical point of view, this has permitted us to administer radioactive iodine in therapeutic amounts which have had a demonstrable cancericidal effect.

Although none of the endocrine treatments of cancer discussed have been demonstrated to have lasting curative effects, I believe that these considerations on the hormonal influences on cancer can be considered as major and important steps towards ultimate understanding and rational treatment of these diseases.

SUMMARY

It has been demonstrated that the administration of estrogenic hormones to experimental animals results in the production of tumors of the following tissues: breast, cervix, uterus, testes and lymph nodes. It has been demonstrated that the administration of pituitary hormones or the

induction of increased elaboration of certain pituitary hormones results in the development of uterine placentomas, ovarian, lymphatic, lung, adrenal, breast, testicular and thyroid tumors.

It has also been demonstrated that by altering the hormonal environment, the following human tumors can be made to recede or to function like normal tissues, prostate, breast (male and female), lymphatic and thyroid. These observations are being further investigated for clues which may ultimately lead to physiologic methods of controlling the development and course of such tumors.

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